REMARKS

Upon entry of the amendments provided herein, claims 1-3, 7 and 8 will be pending. Claim 1 has been amended to recite SEQ ID NO:1 which finds specific support in Example 17 and throughout the specification. Claims 4-6 have been cancelled. Amendments and cancellations are entered without prejudice or disclaimer.

Rejection under 35 USC § 112 – Written Description

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The Examiner states that "[a]lthough the instant specification provides enabled working examples for an antisense oligonucleotide...the antisense oligonucleotide is not a representative sample of the genus of the term 'oligonucleotide'" and therefore, "one skilled in the art cannot determine whether the inventor was in possession of the invention of 'any type of oligonucleotides targeted to human ICAM-1 mRNA' as claimed." Applicant disagrees with the Examiner's assertion, however, in order to advance prosecution of this case, claim 1 is amended herein to recite "antisense oligonucleotide." The rejection is, therefore, rendered moot.

Rejection under 35 USC § 112 – Enablement

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph. The Examiner alleges that the specification "does not reasonably provide enablement for a method of treating pouchitis in a human in need thereof comprising any other formulations or any other nucleic acid compositions" other than one "comprising an antisense oligonucleotide of SEQ ID NO: 1 that is 20 nucleotides in length, further comprising a pharmaceutical excipient, hydroxypropylmethylcellulose, in an enema formulation." Applicant disagrees. However, to further prosecution claim 1 has been amended to recite an "antisense oligonucleotide of SEQ ID NO: 1."

With regard to the Examiner's contention that the method is not enabled for any other formulation than hydroxypropylmethylcellulose, applicant disagrees. Hydroxypropylmethylcellulose is simply one of many pharmaceutical carrier compounds that may

be used in various alimentary delivered formulations including rectal formulations. Specifically, the specification states at paragraph [0045] that a "'pharmaceutical carrier' or 'excipient' is a pharmaceutically acceptable solvent, suspending agent or any other pharmacologically inert vehicle for delivering one or more nucleic acids to an animal...Typical pharmaceutical carriers include, but are not limited to, binding agents (*e.g.*, pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose, *etc.*); fillers (*e.g.*, lactose and other sugars, microcrystalline cellulose, pectin, gelatin, calcium sulfate, ethyl cellulose, polyacrylates or calcium hydrogen phosphate, *etc.*); lubricants (*e.g.*, magnesium stearate, talc, silica, colloidal silicon dioxide, stearic acid, metallic stearates, hydrogenated vegetable oils, corn starch, polyethylene glycols, sodium benzoate, sodium acetate, *etc.*); disintegrants (*e.g.*, starch, sodium starch glycolate, EXPLOTAB); and wetting agents (*e.g.*, sodium lauryl sulphate, *etc.*). Paragraph [0137] further describes the use of enteric carrier material for alimentary administrations. Such material functions to protect the nucleic acid from pH extremes or release the nucleic acid over time to optimize delivery to a particular mucosal site. Such enteric material is known in the art and includes hydroxypropyl methylcellulose as well as many other compounds such as acetate phthalate, propylene glycol, sorbitan monoleate, cellulose acetate phthalate (CAP), and cellulose acetate trimellitate. Paragraph [0145] further provides that "[p]harmaceutically acceptable organic or inorganic carrier substances suitable for non-parenteral administration which do not deleteriously react with nucleic acids can be used. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like."

Further, the knowledge in the skill is high with regard to alimentary formulations. For example in paragraph [0138] it is stated that "methods for producing formulations for alimentary delivery are well known in the art. See, generally, Nairn, Chapter 83; Block, Chapter 87; Rudnic *et al.*, Chapter 89; Porter, Chapter 90; and Longer *et al.*, Chapter 91 *In: Remington's Pharmaceutical Sciences*, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, PA, 1990. The compositions of this invention can be converted in a known manner into the customary

formulations."

Therefore, based on the scope of the claims, disclosure in the application and general knowledge in the art, it would be readily understood by one of skill in the art that many similar pharmaceutical carrier compounds other than hydroxypropylmethylcellulose could be used in rectal formulations of ICAM-1 oligonucleotides. It would not require undue experimentation as these carrier compounds function similarly to deliver the oligonucleotide to the mucosa. As seen in Example 14, "**Evaluation of Enema Formulations for Local Delivery of Oligonucleotide**," effective local colonic delivery of oligonucleotide can be achieved with a variety of formulations. Even oligonucleotide that was merely suspended in sterile saline or water were effective. The Example reiterates that HPMC is a protective colloid that is useful as a general dispersing and thickening excipient and that other compounds can be used for this purpose such as cocoa butter.

Further, it would also be readily understood by one of skill in the art that many different rectal formulations could be employed in a method of treating pouchitis other than enema formulations and that such formulations may depend on a number of factors such as age and medical condition of the patient. For example, the specification provides at paragraph [0030] that "[r]ectal suppositories, retention enemas or rectal catheters can be used for [the] purpose [of administering a rectal formulation] and may be preferred when patient compliance might otherwise be difficult to achieve (*e.g.*, in pediatric and geriatric applications, or when the patient is vomiting or unconscious)." Additionally, the level of skill in the art is such that it would be predictable that other methods of rectal administration could be could be successfully used to deliver an antisense oligonucleotide to treat pouchitis. Specifically, Example 14 states that dispersing carrier agents such as HPMC and cocoa butter may be used in suppository formulations comprising oligonucleotides and that other additives, such as Carrageenan and TPGS, Tween 80, or Sorbitol that may be used as fillers for such suppository formulations were shown not to hinder the localized rectal delivery of oligonucleotides.

Therefore, based on the scope of the claims, disclosure in the application and general knowledge in the art, it would be readily understood by one of skill in the art that rectal formulations other than enema formulations could be used successfully and would not require

undue experimentation.

With regard to formulations containing penetration enhancers in claims 7 and 8, the examiner states that the in vivo rat studies demonstrating increased bioavailability of ISIS 2302 in formulations containing penetration enhancers would not allow one skilled in the art to extrapolate the improved pharmacological effects of such formulation in a human suffering from pouchitis. Applicant respectfully submits that the test is not whether the effects can be directly extrapolated but whether undue experimentation is required. In this case, based on the disclosure which provides a lot of direction and guidance in the form of working examples and based on the level of skill in the art, undue experimentation is not required. The Example section (specifically examples 10 and 11) provides information regarding various penetrations enhancers and there compatibility with antisense oligonucleotides. The examples further provide a number of different formulations containing various combinations of penetration enhancers together with the claimed antisense oligonucleotide and demonstrated increased bioavailability in rat and dog (see examples 10, 11 and 25). Further guidance is provided throughout the specification (see paragraphs [0036] to [0043]). Additionally, the relative skill in the art is recognized to be high. For example, paragraph [0019] states that penetration enhancers have been used to improve the bioavailability of certain drugs and cites Muranishi, *Crit. Rev. Ther. Drug Carrier Systems*, 1990, *7,* 1 and Lee *et al.*, *Crit. Rev. Ther. Drug Carrier Systems*, 1991, *8,* 91. Based on the numerous in vivo working examples, the guidance in the specification and the level of skill in the art, it would be readily understood by one of skill in the art that the use of penetration enhancers in oligonucleotide formulations could be used successfully improve bioavailability and would not require undue experimentation.

Rejection under 35 USC § 112 – Indefiniteness

Claims 1-3 and 7-8 are rejected as being indefinite because it is allegedly unclear which ICAM-1 mRNA sequence is targeted by the instantly claimed pharmaceutical compostion comprising an oligonucleotide. Claim 1 has been amended to recite an antisense oligonucleotide of SEQ ID NO: 1 therefore the rejection is rendered moot.

Double Patenting

Applicant requests that the double patenting rejection be held in abeyance until such time as allowable subject matter is identified in this case.

FEES

The fee for a three month extension of time is included with this response. It is believed that no additional fee is due. However, if an additional fee is due, the Commissioner is herby authorized to charge the Deposit Account 50-0252 referencing case number FMDL0001US.

CONCLUSIONS

In view of these amendments and remarks, the Applicants believe that the case is now in proper form for allowance. Prompt issuance of a Notice of Allowance is respectfully requested. If the Examiner believes that outstanding issues remain in the case, the Examiner is encouraged to call the undersigned Agent for Applicant listed below to discuss the matter.

Respectfully submitted,

Date: 3/22/07

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